Parental Occupation and Childhood Cancer: Review of Epidemiologic Studies

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Parental occupational exposures might affect childhood cancer in the offspring through genetic changes in the ovum or sperm or through transplacental carcinogenesis. The 24 published epidemiologic studies of this association have all used case-control designs, with controls generally selected from birth certificates or from general population sampling. Occupational exposures were inferred from job titles on birth certificates or through interviews. A large number of occupation-cancer associations have been reported, many of which were not addressed or not confirmed in other studies. Several associations have been found with consistency: paternal exposures in hydrocarbon-associated occupations, the petroleum and chemical industries, and especially paint exposures have been associated with brain cancer; paint exposures have also been linked to leukemias. Maternal exposures have received much less attention, but studies have yielded strongly suggestive results linking a variety of occupational exposures to leukemia and brain cancer. The primary limitations in this literature are the inaccuracy inherent in assigning exposure based on job title alone and imprecision due to limited study size. Although no etiologic associations have been firmly established by these studies, the public health concerns and suggestive data warrant continued research.

Introduction

In spite of numerous epidemiologic studies of parental occupation and childhood cancer, no clear causal associations have been established (1,2). In fact, the only established human carcinogen that acts through either parent is diethylstilbestrol, a drug administered during pregnancy that causes vaginal adenocarcinoma in female offspring (3). It happens that the resulting vaginal cancer does not appear during childhood, but this agent establishes the plausibility of transplacental exposures affecting human cancer risk. In utero exposure to diagnostic X-rays is strongly suspected of causing leukemia during childhood (4), but the association remains controversial (5).

The evidence that parental occupational exposures can adversely affect reproductive outcomes other than cancer is persuasive (1,6). Exposures to males can cause infertility (7) and possibly miscarriages among wives of exposed workers (8,9). Pregnant women who work with anesthetic gases appear to have an excess of miscarriages (10,11) as do nurses exposed to chemotherapeutic drugs used in cancer treatment (12). Studies of parental occupation and childhood cancer are predicated on the limited evidence linking other parental exposures (drugs, X-rays) to childhood cancer combined with the

stronger indications that agents in the workplace can adversely affect reproduction (13).

Potential mechanisms for an effect of parental occupational exposures specifically on childhood cancer are speculative. Preconception maternal exposures might have genetic effects that alter the offspring's susceptibility to cancer, although the ovum appears to be relatively protected from exogenous agents (14).

Transplacental carcinogenesis is a more likely mechanism through which in utero exposures would influence the later development of cancer. As noted earlier, diethylstilbestrol remains the only established human transplacental carcinogen, but extensive laboratory evidence (15) supports the plausibility of environmental agents operating in this manner and suggests that prenatal exposures may be more potent than postnatal exposures. The evidence for transplacental toxicity is clear for maternal exposure to teratogens such as lead and alcohol (14). Enhanced susceptibility to cancer during childhood could be viewed as a type of congenital anomaly produced by maternal exposure to workplace teratogens. Nonetheless, a series of assumptions is required to argue for the plausibility of an etiologic role of maternal occupational exposures in childhood cancer.

The potential mechanisms through which male occupational exposures might affect the offspring's risk of cancer are far more tenuous. One possible pathway is for the father to bring toxic exposures into his home (16) and thereby expose his wife and, transplacentally, the fetus. Such an indirect route could only occur for nonvolatile chemical agents such as lead. Whether the

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dose of a toxic agent would be sufficiently large to reach the wife and then the fetus in appreciable quantities is questionable.

A biologically interesting but far more speculative mechanism is a genetic alteration in the father's sperm that would transmit an enhanced cancer susceptibility to his child. Genetic syndromes, which include specific types of childhood malignancies such as certain forms of retinoblastoma or Wilms' tumor, are well documented (17), and the paternal genome clearly can contribute to this risk. Sperm are genetically susceptible to environmental agents (18). Epidemiologic evidence for paternally mediated reproductive effects other than infertility, however, is quite limited. No paternal exposure (drugs, tobacco, radiation, or environmental chemicals) has been proven to cause miscarriage, congenital defects, or childhood cancer (6,13). Laboratory evidence suggests that paternal exposures to rats can affect fetal loss and malformations (19), growth (20), and even subsequent cancer risk (21) without altering fertility. Examination of exposures that might genetically alter sperm to enhance the risk of cancer in the offspring of humans thus has some experimental basis, but a well-defined biological basis for paternal exposures increasing the risk of childhood cancer is absent.

In spite of a somewhat tenuous biological rationale, the association of parental occupation and childhood cancer has received substantial interest. The methods and results of the 24 epidemiologic evaluations of parental occupation and childhood cancer that were found in the literature up to October 1989 (22–45) are reviewed. The literature is essentially a collection of unrelated empirical observations that are not well-suited to a condensed narrative summary (2), so detailed tables have been provided. Relative to an earlier review (46), the volume of literature has grown and a more systematic approach to the classification of study results was developed. As studies proliferate, it will be important to identify those associations that are sufficiently consistent and plausible to deserve the intensive effort that will ultimately be required to establish or refute suggestions of causality.

Methods of Review

All published literature that directly assessed parental occupation and any form of childhood cancer in humans was included. Although the primary interest was on chemical and physical hazards in the workplace, occupations not likely to incur such exposures were also considered. Study methodologies were summarized and results were tabulated according to the exposed parent (father, mother), the type of childhood cancer studied (total, leukemias and lymphomas, nervous system, and urinary tract), and the nature of the occupational exposure (hydrocarbons, metals, etc.). Odds ratios addressing similar associations were tabulated in chronological order by the year of publication.

Results for a specific occupation-cancer association were tabulated whenever one or more of three conditions was met: a) the odds ratio was 1.5 or greater based on 10 or more exposed cases or 5 or more discordant pairs; b) the odds ratio was statistically significantly elevated ($p < 0.05$); or c) another study provided an association that met conditions a or b and data pertaining to that association were reported based on 5 or more exposed cases and 3 or more discordant pairs in another study. The goal was to include suggestive associations, requiring a certain minimum study size and a minimally elevated odds ratio. If such an association was observed in at least one study, the criteria for including potential corroborative or contradictory evidence was relaxed in order to fully examine the consistency of the observation. Some studies failed to provide a complete array of results, instead tabulating only those that were statistically significant (34,45). Unfortunately, the effect estimates for such nonsignificant associations could not be included.

In some instances, odds ratios had to be calculated from data provided in the articles (22–24,28). In these calculations, the occupation of interest was considered exposed and all other occupations were considered unexposed. To minimize redundancy in the tables and provide comparable data across studies, several additional rules were imposed. Some studies provided risk estimates based on different time periods of exposure (28,31,32,41), but only occupational data nearest the time of birth are presented. Two studies provided risk estimates for different calendar time periods (25,26), but only the values for the total study period were tabulated. Most studies considered alternative definitions of occupational exposure based on industry, occupation, aggregated industries or occupations, etc. The narrowest occupational groupings are presented, although this goal was sometimes relaxed to include substantially elevated relative risk estimates and to avoid tabulating closely overlapping categories.

Results

Study Methods

Table 1 summarizes the constitution of the study groups, exposure definitions, and confounders included in these 24 studies. Interest in this topic has recently expanded: only two of the studies were published before 1980 versus 15 in 1984 or later. All of the studies used case-control sampling, with the proportionate mortality analysis of Sanders et al. (26) interpretable as a case-control study in which the control group consists of all decedents (47).

The age range of cancer cases varied markedly across studies, with upper age limits ranging from 1 (29) to 24 years old (36). Vianna et al. (29) postulated that the earliest cancers are more likely to be affected by in utero exposures. Most studies have been conducted in the United States, with one each in Canada, Finland, England and Wales, the Netherlands, and China (Table 1). Although the biological relationships of interest would not be expected to differ as a function of geographic

Table 1. Case and control groups, exposure definition, and confounders in studies of parental occupation and childhood cancer.

Reference	Study location and study period	Case group	Upper age limit, years	Number of cases	Source of controls	Source of exposure information	Time period of exposure	Potential confounders considered
Total cancers								
(22)	Quebec, 1965–1970	Cancer deaths	4	386	Birth certificates	Father's occupation on birth certificate	At birth	Parents' ages, residence
(23)	Massachusetts, 1947–1957, 1963–1967 births	Cancer deaths	14	692	Birth certificates	Father's occupation on birth certificate	At birth	Parents' ages, sex, and race of child
(24)	Houston area, 1976–1977	Cancer cases	15	296	Clinic records, case parent siblings, neighborhood	Parents' occupational histories from interview	Year before birth through diagnosis	Father's age, parents' education
(25)	Finland, 1959–1975	Cancer cases	14	948	Birth certificates	Parents' occupation in welfare center records	During pregnancy	Parents' ages, birth order, birth weight, residence
(26)	England and Wales, 1959–1963, 1970–1972	Cancer deaths	14	6920	All childhood deaths	Father's occupation on child's death certificate	At death	Social class
(27)	Houston area, 1976–1977	Cancer cases	15	298	Clinic records, case parent siblings, neighborhood	Parents' occupational histories from interview	Year before birth	None
Leukemias and lymphomas								
(28)	Baltimore SMSA, 1965–1974 (brain), 1969–1974 (leukemia)	Brain tumor and leukemia cases	19	43 (brain) 70 (leukemia)	Birth certificates, other cancer cases	Parents' occupational histories from interview	Before birth through diagnosis	Sex, year of birth, race
(29)	New York State (outside New York City), 1949–1978	Acute leukemia cases	1	65	Birth certificates	Parents' occupational histories from interview	Before birth	Year of birth, sex, race, county, parents' ages, birth order, maternal education, X-rays, other exposures
(30)	California, 1975–1980	Leukemia cases	15	255	Birth certificates	Father's occupation on birth certificate	At birth	Parents' ages, child's race, sex, and birth order
(31)	Netherlands, 1973–1979	Acute lymphocytic leukemia cases	14	519	Population-based	Parents' occupational histories from questionnaire	During pregnancy and 1 year before birth	Age, sex, residence, birth order, social class
(32)	Los Angeles County, 1980–1984	Acute leukemia cases	10	123	Case friends and random digit dialing	Parents' occupational histories from interview	1 year before conception to 0.5 or 1 year before diagnosis	Parents' smoking, drinking, diet, mother's medications, child's age, sex, race, ultrasound, X-ray exposure
(33)	Shanghai, China, 1974–1986	Leukemia cases	15	309	Neighborhood	Parents' occupational histories from interviews	Before conception and during pregnancy	Age, sex, birth weight, birth order, residence, X-rays, medications, mother's age at menarche
(34)	U.S. and Canada, 1980–1984	Acute nonlymphocytic leukemia cases	18	204	Random digit dialing	Parents' occupational histories from interview	Lifetime	Age, race

Table 1. *Continued.*

Reference	Study location and study period	Case group	Upper age limit, years	Number of cases	Source of controls	Source of exposure information	Time period of exposure	Potential confounders considered
Nervous system								
(35)	Los Angeles County, 1972–1977	Brain tumor cases	9	98	Case friends, neighbors	Parents' occupational histories from interview	Year before birth through diagnosis	Mother's smoking, drugs, alcohol, hair dyes, foods during pregnancy
(36)	Los Angeles County, 1972–1977	Brain tumor cases	24	226	Case friends, neighbors	Parents' exposures from interview	Before birth to before diagnosis	Numerous parent and child characteristics
(37)	Texas, 1964–1978	Neuroblastoma deaths	14	157	Birth certificates	Father's occupation on birth certificate	At birth	Parents' ages, residence, prenatal care, marital status, child's sex, ethnicity
(38)	Western Washington State, 1978–1981	Brain tumor cases	16	51	Random digit dialing and area sampling	Father's occupational exposure from interview	1 yr. before birth to diagnosis	Parents' ages, smoking, drinking patterns, mother's exposure to chemicals, child's sex, age, race
(39)	Texas, 1964–1980	Intracranial and spinal cord tumor deaths	15	499	Birth certificates	Father's occupation on birth certificate	At birth	Child's age, sex, race, birth weight, birth order, gestational age, parents' ages, residence, prenatal care, etc.
(40)	Ohio, 1959–1978	Brain tumor deaths	19	491	Birth certificates	Father's occupation on birth certificate	At birth	Sex, race, year of birth, parents' ages, birth weight, birth order, county
(41)	New York State (outside New York City), 1968–1977	Central nervous system tumor cases	15	338	Birth certificates	Parents' occupation and industry history from interview of mothers	At birth and at diagnosis	Child's age, sex, race, parents' ages, religion, education, nativity
Urinary system cancers								
(42)	Connecticut, 1935–1973	Wilms' tumor cases	19	149	Birth certificates	Father's occupation on birth certificate	At birth	Social class, birthplace, pregnancy history, parents' ages and birthplace, birth weight, length of gestation
(43)	Columbus, Ohio area, 1950–1967	Wilms' tumor cases	None	62	Birth certificates	Father's occupation on birth certificate linked to exposure	At birth	Age, sex, race, birth weight, parents' ages, birth order, county
(44)	Columbus, Ohio area, 1950–1967	Wilms' tumor cases	None	62	Birth certificates	Father's occupation on birth certificate	At birth	Age, sex, race, birth weight, parents' ages, birth order, county
(45)	Philadelphia area, 1970–1983	Wilms' tumor cases	15	88	Random digit dialing	Parents' occupational exposures from telephone interview	18 years old to 6 months before diagnosis	Age, race

location, the range of occupations covered and the implications of a given job title for specific exposures might differ. For example, Peters et al. (35) focused on aircraft industry employment in their study of brain tumors due to the concentration of this industry in the Los Angeles area. Their findings could not be addressed in studies in Massachusetts (23), Baltimore (28), or Ohio (40) because of the rarity of such employment in those areas. If work conditions vary, for example, between the United States and China, then the exposure implications of a given job title (e.g., machinist, textile worker) could produce discrepant results.

The earliest eligibility dates for case diagnoses ranged from 1935 (42) to 1980 (32,34) with the end of eligibility ranging from 1967 (43,44) to 1986 (33) (Table 1). Exposures associated with a particular occupational title might be expected to differ over time as industrial processes and exposure standards change. In general, work environments have improved over time so that a failure to observe excess risk in more recent periods may not negate the causal implications of excess risks observed in earlier time periods.

The cancer type and vital status of cases (incident versus deceased) varied across the studies (Table 1). Variations in the composition of case groups could affect study results since the determinants of childhood cancer may be specific to the cancer type (48). If parental occupation influenced survival by affecting access to health care, for instance, then the studies of deceased cases might reach invalid conclusions regarding etiologic associations.

Case groups ranged in size from 43 brain tumor cases (24) to Sanders 6,920 cancer deaths (26) (Table 1). Because study group size is as important a determinant of the p-values as the magnitude of effect, a given odds ratio from a large study will attain significance more readily than that from a smaller study. The statistical significance of findings is therefore not emphasized in the interpretation of results.

Controls were usually derived from birth certificates or sampled from the general population (Table 1). Controls who were ill were included in three studies (24,27,28) in an attempt to minimize reporting bias among parents of children who had severe health problems. To adequately reflect the exposure distribution in the underlying population at risk, however, it must be assumed that exposure is unrelated to the controls' diseases and that those children with illnesses other than cancer come from the same base population.

Exposure was established based on occupation in birth certificates (9 studies), interviews (12 studies), medical records (1 study), death certificates (1 study), or questionnaires (1 study). Studies that rely on recorded data from birth certificates, medical records, or death certificates have the virtue of unbiased ascertainment but provide no control over the accuracy or level of detail of the information provided. Interviews provide an opportunity for more detailed discussion of specific exposures with some potential for respondent or interviewer bias, although it is not likely that parents'

suspicions would lead to misreporting of occupation. Given the relative ease of obtaining occupational titles from birth certificates, it is unfortunate that none of the studies that selected controls from birth certificates and conducted personal interviews to ascertain exposure (28,41) addressed the comparability of exposure information from these two data sources. Relative to the true exposures of interest, both certificates and interview information are obviously imperfect to an unknown but probably substantial degree.

Studies that relied on birth certificates for exposure information could only consider exposures near the time of birth. Interview studies were able to examine exposures in the period preceding birth (generally 1 year) as well as the period preceding the child's diagnosis. In principle, different mechanisms of effect (i.e., a preconception genetic effect, in utero exposure, or postnatal exposure to the child) could be identified in the latter studies, but the job stability throughout the interval, especially for fathers, limits such analyses.

The potential confounders available for consideration largely reflect the mode of data acquisition (Table 1). Certificate-based studies only had access to demographic information, including parental ages, race, residence, and education, child's sex, and mother's pregnancy history. Interview studies generally obtained information on parental occupation as well as many other potential risk factors, so that other potential determinants of cancer risk could be examined as confounders. Given the paucity of information on etiologic factors in childhood cancer (48), it is difficult to argue that confounding occurred in studies with less extensive data on extraneous factors. Adjustments for potential confounders such as parents' ages, child's sex, race, and birth weight generally did not change the results markedly.

Study Results

Table 2 summarizes the results of studies of paternal exposures and total childhood cancer, including the initial report by Fabia and Thuy (22). Most studies have focused on exposures to hydrocarbons and other industrial chemicals. Two studies reported odds ratios of two or greater for mechanics (22,27), with contradictory results from Kwa and Fine (23). Odds ratios of 2 to 5 were observed by Hicks et al. (27) for aircraft workers and radiation-exposed military workers. Sporadic elevations in odds ratios were found for machinists, printers, and farmers, based on a single study with nonsupportive results reported in one or more investigations. None of the studies reporting results for hydrocarbons warranted inclusion based on the criteria defined earlier.

A noteworthy finding in Table 2 is the suggestive risk increases associated with occupations in which toxic exposures are not expected, such as men with an academic degree (25) and professionals, administrators, and clerical workers (26). These associations may reflect the increased incidence of childhood leukemias in the higher social classes (48), and serve as a reminder that occu-

Table 2. Results of studies of paternal occupation and total childhood cancer.

Occupation	Number of exposed cases	Odds ratio[a]	Reference
Mechanic			
Motor vehicle mechanic	28	2.2[b]	(22)
Mechanic, gas station attendant	35	1.1	(23)
Aircraft mechanics	6	2.3–infinity[*]	(27)
Machinist			
Machinist	24	1.7	(22)
Machinist	71	1.1	(23)
Machinist, miner, lumberman	9	0.5–1.8	(24)
Machine repairman	46[c]	0.9	(25)
Radiation and military			
Radiation related	30	1.5–2.0	(27)
Radiation-exposed military	13	2.1–5.2[*]	(27)
Radar related	21	1.1–2.1	(27)
Armed forces	187	0.8	(26)
Electrical			
Electrician, plumber, carpenter	12	0.9–1.5	(24)
Electrical	209	1.0	(26)
Other industrial exposures			
Printer	15	1.8	(23)
Petroleum industry	22	0.7–1.6	(24)
Aircraft workers	13	3.1[*]–5.2[*]	(27)
Agriculture			
Farmers	450[b]	1.2[*]	(25)
Farmers	274	1.1	(26)
No industrial exposures			
With academic degree	61[b]	1.7[*]	(25)
Professional, technical workers, artists	687	1.4[*]	(26)
Administrators and managers	302	1.7[*]	(26)
Clerical workers	376	1.3[*]	(26)
Sales workers	539	1.3[*]	(26)

[a] Range of odds ratios provided when multiple control groups were used.

[b] Number of exposed cases not provided; number of discordant pairs listed.

[*] $p < 0.05$.

pational titles may be associated with childhood cancer through mechanisms other than environmental exposures.

Studies of paternal occupation in relation to childhood leukemias and lymphomas are summarized in Table 3. Motor vehicle related occupations (mechanics, drivers) were associated with elevated risks in some studies (22,28,32) but not in others (23,31). Machinists and factory workers also showed several associations of 2-fold or greater (22,28,32,34), but the diversity of jobs makes it difficult to evaluate the consistency of the data. Hydrocarbon exposures were strongly related to leukemia in the study by Vianna et al. (29) of cases age 1 year or less. Sanders et al. (26) and Van Steensel-Moll et al. (31) failed to confirm that finding with cases covering a broader age range.

Exposure to paints and pigments yielded the most consistently positive results, with five studies (22, 25,31,32,34) producing odds ratios of 1.5 or greater. Isolated findings implicate plastic and rubber, chlorinated solvents, petroleum products, food and drink manufacturing, and medical and social services.

Nervous system cancers, consisting primarily of brain tumors and neuroblastomas, were examined in a large number of studies (Table 4). The possibility of site-specificity of etiologic agents should be considered in reviewing these results, especially for neuroblastoma compared to brain and central nervous system cancers.

Motor vehicle-related occupations were found to be overrepresented among case fathers by Fabia and Thuy (22) and to a lesser extent by Wilkins and Koutras (40), but not by four other investigators (23,25,37,39). An odds ratio of 4.4 for machine repairmen (25) was not replicated (23,28,39,40). Risk elevations were again noted for painters, with strongly positive results from two studies (ORs = 2.6, 7.0) (25,35) and null results from two others (39,40).

Exposures associated with the chemical and petroleum industries produced reasonably consistent indications of a positive association, with odds ratios of 1.5 or greater in three studies (35,39,41) and of 3.0 or greater in two studies (35,39). Hydrocarbon exposures in the aggregate were only associated with nervous system cancers in the study of neuroblastoma (37) and not in the three studies of central nervous system cancers (26,28,41). Metal-related work was associated with brain cancer, but in only one study (40).

Three studies (37,40,41) found elevated risks associated with assorted electrical occupations. Both Hicks et al. (27) and Nasca et al. (41) found ionizing radiation to be associated with nervous system cancers, with odds ratios around two. Isolated reports implicate metal-related occupations, farming, construction, aircraft industry, printing, and graphic arts in brain cancer risk, though the associations were either not examined or not confirmed in other studies. The three studies that included data on paper and pulp mill workers (23,39,41) all noted increased odds ratios, ranging from 1.6 to 4.0.

Urinary system cancers were the focus of several studies (42–45) (Table 5). Hydrocarbon exposures were implicated by Kantor et al. (42) and Kwa and Fine (23), but not confirmed in other studies (26,41,42). Similarly, lead was rather strongly linked to Wilms' tumor in one study (42) but not others (43,44). Radiation exposure was associated with Wilms' tumor risk in two studies (27,45), each reporting odds ratios of two or greater. Boron has also been identified as a risk factor in two studies (43,45). The plausibility of environmental contaminants acting on the kidney encourages further evaluation of the postulated associations.

Maternal exposures to occupational hazards (Table 6) were addressed in few of the studies, primarily because of the rarity with which mothers had worked in potentially hazardous workplaces. Hemminki et al. (25) found total cancer risk to be associated with work as a pharmacist, farmer, baker, or in the food industry.

Table 3. Results of studies of paternal occupation and childhood leukemias and lymphomas.

Occupation	Cancer site	Number of exposed cases	Odds ratio[a]	Reference
Motor vehicle related				
Motor vehicle mechanic, service station attendant	Leukemia/lymphoma	16	2.0[b]	(22)
Mechanic, gas station attendant	Leukemia/lymphoma	21	1.1	(23)
Motor vehicle driver	Leukemia/lymphoma	28	1.0	(23)
Motor vehicle driver	Leukemia	96[b]	1.5	(25)
Motor vehicle related	Leukemia	6	0.8, infinity*	(28)
Auto mechanic, machinist, gas station attendant, miner	Acute lymphocytic leukemia	18	0.8	(31)
Transportation	Acute leukemia	22[b]	1.4	(32)
Transportation equipment	Acute leukemia	21[b]	2.5*	(32)
Transportation equipment operator	Leukemia	24	1.2	(33)
Machinist and factory worker				
Machinist, miner, lumberman	Leukemia/lymphoma	23	2.5*	(22)
Machinist	Leukemia/lymphoma	49	1.3	(23)
Machine repairmen	Leukemia	15[b]	0.3	(25)
Factory worker, machinist, and related occupations	Leukemia	11	0.8,2.5	(28)
Operators, fabricators, laborers	Leukemia	57	1.1	(30)
Manual and mechanical skills	Acute lymphocytic leukemia	188	1.0	(31)
Machinery	Acute leukemia	20[b]	3.0*	(32)
Aircraft manufacturing	Acute leukemia	17[b]	1.8	(32)
Blacksmiths, toolmakers, etc.	Leukemia	50	0.9	(33)
Nonauto mechanic	Acute nonlymphocytic leukemia	14	3.5*	(34)
Aggregated hydrocarbon				
Hydrocarbon related	Leukemia	202,416	0.9,1.0	(26)
Hydrocarbon related	Leukemia	7,10[b]	1.0,2.5	(28)
Hydrocarbon, high	Acute leukemia	24,28[b]	2.4*,2.5*	(29)
Hydrocarbon, low	Acute leukemia	19,25[b]	1.3,3.8*	(29)
Hydrocarbon related	Acute lymphocytic leukemia	37	1.0	(31)
Paints and pigments				
Painter, dyer, cleaner	Leukemia/lymphoma	5	1.7	(22)
Painter	Leukemia/lymphoma	7	0.9	(23)
Painter	Leukemia	12[b]	1.5	(25)
Painter, cleaner, dyer	Acute lymphocytic leukemia	8	1.6	(31)
Pigments (dyes) exposure	Acute lymphocytic leukemia	25	1.6	(31)
Spray paint	Acute leukemia	26[b]	2.2*	(32)
Dyes, pigments	Acute leukemia	8[b]	3.0	(32)
Painter	Acute nonlymphocytic leukemia	7	7.0*	(34)
Food related				
Baker, cook, restaurant worker	Leukemia/lymphoma	12	1.4	(23)
Food preparation	Leukemia	3[b]	0.5	(30)
Foods and drink manufacturing	Acute leukemia	13[b]	2.2	(32)
Other chemicals				
Tar or asphalt exposure	Acute lymphocytic leukemia	26	1.1	(31)
Petroleum chemicals manufacturing	Acute leukemia	16[b]	1.0	(32)
Petroleum products	Acute nonlymphocytic leukemia	NA[c]	2.8*	(34)
Plastic or rubber exposure	Acute lymphocytic leukemia	25	2.0	(31)
Chemical, rubber, and plastics workers	Leukemia	12	1.1	(33)
Plastics	Acute nonlymphocytic leukemia	NA	1.5	(34)
Chlorinated solvents	Acute leukemia	13[b]	2.2	(32)
Solvents	Acute nonlymphocytic leukemia	NA	2.1*	(34)
Other occupations				
Medical and social services	Acute lymphocytic leukemia	18	2.8*	(31)
Medical and public health workers	Leukemia	5	0.6	(33)

[a] Range of odds ratios provided when multiple control groups were used.
[b] Number of exposed cases not provided; number of discordant pairs listed.
[c] NA, not available.
*p < 0.05.

Table 4. Results of studies of paternal occupation and childhood nervous system cancers.

Occupation	Cancer site	Number of exposed cases	Odds ratio[a]	Reference
Motor vehicle related				
Motor vehicle mechanic, service station attendant	Nervous system	10	2.8*	(22)
Mechanic, gas station attendant	Nervous system	6	1.0	(23)
Motor vehicle driver	Nervous system	5	0.6	(23)
Motor vehicle driver	Brain	84[b]	0.9	(25)
Transportation, utilities, communication	Neuroblastoma	12	0.9	(37)
Motor vehicle mechanic, service station attendant	Nervous system	NA[c]	0.7	(39)
Motor freight and transportation	Brain	37	1.6	(40)
Machinist and factory worker				
Machinist	Nervous system	9	0.7	(23)
Machine repairman	Brain	14[b]	4.4*	(25)
Factory worker, machinist, and related occupations	Brain	16	0.7,2.5	(28)
Factory worker, machinist, and steelworker	Nervous system	NA	1.2	(39)
Machine trades occupations	Brain	66	1.2	(40)
Paint				
Painter	Brain	14[b]	2.6	(25)
Paint exposure	Brain	7	7.0*	(35)
Painter	Nervous system	NA	1.0	(39)
Painting, plastering, etc.	Brain	7	1.2	(40)
Chemicals				
Chemical solvent exposure	Brain	20	2.8*	(35)
Chemical industry	Nervous system	12	1.4	(39)
Chemical workers	Nervous system	6	0.8	(39)
Chemical and petroleum refinery worker	Nervous system	9	3.0*	(39)
Chemical and drug salesman	Nervous system	5	10.0*	(39)
Chemical industry	CNS tumors	10	1.5	(41)
Petroleum industry				
Oil and gas extraction	Neuroblastoma	8	1.3	(37)
Petroleum refinery worker	Nervous system	6	2.0	(39)
Petroleum industry	CNS tumors	9	3.1	(41)
Aggregated hydrocarbon				
Hydrocarbon related	Brain	419	0.9	(26)
Hydrocarbon related	Brain	11	0.5,2.3	(28)
Aromatic hydrocarbons, nonionizing radiation	Neuroblastoma	5	1.8	(37)
Aromatic and aliphatic hydrocarbons	Neuroblastoma	10	3.2*	(37)
Hydrocarbon related, narrow definition	CNS tumors	18	1.3	(41)
Hydrocarbon related, broad definition	CNS tumors	38	1.4	(41)
Electrical				
Electronics workers	Neuroblastoma	6	11.8*	(37)
Electrical assembling, installing, and repairing	Brain	19	2.7*	(40)
Electromagnetic fields, narrow definition	CNS tumors	15	1.7	(41)
Electromagnetic fields, broad definition	CNS tumors	19	1.6	(41)
Ionizing radiation				
Industrial, less exposure	Nervous system	10	1.0–1.1	(27)
Occupation, less exposure	Nervous system	7	1.8–2.1	(27)
Industrial, more exposure	CNS tumors	28	2.2*	(41)
Industrial, less exposure	CNS tumors	61	1.7*	(41)
Occupation, more exposure	CNS tumors	19	1.0	(41)
Occupation, less exposure	CNS tumors	31	1.1	(41)
Metals				
Metal processors and producers	Brain	62	1.8*	(40)
Welders, cutters	Brain	11	2.7	(40)
Metal working occupations	Brain	14	1.6	(40)

Table 4. *Continued.*

Occupation	Cancer site	Number of exposed cases	Odds ratio[a]	Reference
Agriculture				
Farmer	Nervous system	6	0.6	(22)
Farmer	Brain	107[b]	1.2	(25)
Agriculture	Neuroblastoma	6	0.6	(37)
Farming and agricultural occupations	Brain	30	2.0[b]	(40)
Construction				
Construction	Neuroblastoma	17	0.9	(37)
Construction industry	Brain	47	2.3[*]	(40)
Construction occupations	Brain	26	2.0[*]	(40)
Carpenters	Brain	14	1.9	(40)
Paper and pulp mill				
Paper and pulp mill	Nervous system	6	2.8[*]	(23)
Paper and pulp mill worker	Nervous system	NA	4.0	(39)
Pulp and paper industry	CNS tumors	8	1.6	(41)
Aerospace and aircraft industries				
Aircraft industry	Brain	12	Infinity[*]	(35)
Aerospace occupation	Brain	7	1.1	(38)
Aircraft industry worker	Nervous system	NA	1.0	(39)
Other occupations				
Printing workers	Nervous system	9	4.5[*]	(39)
Graphic arts workers	Nervous system	5	21.9[*]	(39)
Glass, clay, stone industry	Brain	12	1.5	(40)

[a] Range of odds ratios provided when multiple control groups were used.
[b] Number of exposed cases not provided; number of discordant pairs listed.
[c] NA, not available.
[*] $p < 0.05$.

Table 5. Results of studies of paternal occupation and childhood urinary system cancers.

Occupation	Cancer site	Number of exposed cases	Odds ratio[a]	Reference
Hydrocarbon related				
Motor vehicle mechanic	Wilms' tumor	6	6.2	(42)
Machinist	Wilms' tumor	5	1.7[*]	(42)
Mechanic, gas station attendant, machinist	Urinary tract	10	2.6[*]	(23)
Machinist	Wilms' tumor	9	3.2	(45)
Hydrocarbon related	Kidney	111	1.2	(26)
Soot exposure	Wilms' tumor	16	0.8	(43)
Hydrocarbon related	Wilms' tumor	10	1.4	(44)
Benzo(a)pyrene exposure	Wilms' tumor	15	0.8	(43)
Lead exposure				
Lead related	Wilms' tumor	22	3.7[*]	(42)
Lead exposure	Wilms' tumor	18	1.1	(43)
Lead related	Wilms' tumor	11	1.3	(44)
Radiation related				
Radiation-related industry	Wilms' tumor	13	2.5[*]–2.6[*]	(27)
Radiation	Wilms' tumor	15[b]	2.0	(45)
Radium	Wilms (nongenetic)	5[b]	4.0	(45)
Other occupational exposures				
Trichloroethylene exposure	Wilms' tumor	10	1.5	(43)
Boron exposure	Wilms' tumor	7	3.5[*]	(43)
Boron	Wilms (genetic)	5[b]	Infinity	(45)
Dichloroethyl ether	Wilms (genetic)	5[b]	4.0	(45)
Nitroparaffins	Wilms (genetic)	6[b]	5.0	(45)

[a] Range of odds ratios provided when multiple control groups were used.
[b] Number of exposed cases not provided; number of discordant pairs listed.
[*] $p < 0.05$.

Table 6. Results of studies of maternal occupation and childhood cancer.

Occupation	Number of exposed cases	Odds ratio	Reference
Total cancers			
Pharmacist	12[a]	3.2*	(25)
Agriculture, gardening, forestry	29[a]	1.7	(25)
Food industry	37[a]	2.1*	(25)
Baker	20[a]	2.4	(25)
Leukemia			
Pharmacist	5[a]	2.6	(25)
Pharmacist	NA[b]	19.7*	(33)
Medical and social services	21	1.0	(31)
Physicians	NA	5.7*	(33)
Manual and mechanical skills	15	2.0	(31)
Blacksmiths, toolmakers, etc.	32	1.1	(33)
Metal refining and processing	8	2.6	(33)
Lead	5	2.3	(33)
Metal dusts	NA	3.0	(34)
Textile industry	8	4.2*	(31)
Textile workers and tailors	27	0.7	(33)
Chemical exposure	25	2.4*	(31)
Chemical processors	25	3.3*	(33)
Hydrocarbon related	7	2.5	(31)
Benzene	24	2.0	(33)
Gasoline	38	1.6	(33)
Toluene	20	1.5	(33)
Kerosene	16	1.6	(33)
Diesel oil	16	1.6	(33)
Pigment (dyes) exposure	22	1.8	(31)
Paints and pigments	Not stated	1.5	(34)
Personal service industries	12	2.7*	(32)
Service workers	34	1.4	(33)
Domestics, hotel, and catering	24	2.8*	(31)
Agriculture and forestry	12	2.3	(33)
Pesticides	12	3.5	(33)
Pesticides	NA	6.0*	(34)
Brain cancer			
Chemicals on skin	10	3.3	(33)
Inhaled chemicals or fumes	13	3.0	(33)
Baker	9[a]	1.6	(25)
Wore protective clothing or equipment (exposure proxy)	15[a]	4.0*	(34)
Wilms' tumor			
Aromatic amino compounds	5[a]	Infinity	(45)

[a] Number of exposed cases not provided; number of discordant pairs listed.
[b] NA, not available.
* $p < 0.05$.

Occupations found more frequently among mothers of children with leukemia included a wide variety of chemical exposures. Notably strong or replicated associations were found for work as a pharmacist (25), in metal manufacturing or processing (33,34), textiles (31), pigments (31,34), or unspecified chemicals (31,33). Studies of maternal occupation and brain cancer (33,34) produced strong positive associations with chemical hazards in general (ORs of 3.0–4.0). Unfortunately, there is very limited opportunity to have these results corroborated given the few studies of maternal occupation.

Discussion

In spite of a large number of studies, no specific parental occupational exposure has been established as a cause of childhood cancer. However, several paternal occupations have been found to be associated with childhood leukemias and nervous system tumors and maternal occupations with several cancers based on the magnitude of odds ratios and replication in two or more studies. The most promising leads for further study are paternal paint exposure and to a lesser extent paternal hydrocarbon exposure in relation to both childhood leukemias and brain cancer. Paternal work with ionizing radiation and work in the petroleum, chemical, electrical, and paper industries should be further evaluated in relation to childhood brain cancer. Maternal exposures have received relatively little attention, but the few studies have yielded strongly suggestive results implicating a variety of occupational chemicals in leukemia and brain cancer.

There was a tendency for specific studies to produce many elevated or many null odds ratios, with no clear methodological basis given their methodological similarity (Table 1). The most parsimonious explanation for generating an array of positive associations with industrial exposures would be having selected an unsuitable control group. False negative results are also readily accounted for by poor exposure assessment or overly broad groupings of disease.

Positive results were more common in studies of nervous system cancers (Table 4) than studies of leukemia (Table 3) or urinary system cancer (Table 5), either reflecting more causal relationships or superior study methods. Again, there is no obvious pattern based on the study attributes summarized in Table 1.

There are several important methodological limitations pervasive in this literature that would tend to obscure associations. Exposure classification is the most critical. The exposures of ultimate interest are specific physical or chemical agents in the workplace that reach the parent. The ability of the surrogates used in these studies (typically a job title alone) to accurately identify exposed and unexposed individuals is highly questionable. The associations are virtually all between occupation and childhood cancer, not actually between an occupational exposure and childhood cancer. Job titles may not accurately identify exposures due to errors in reporting, but especially due to the inherent variability in activities and environments associated with any given job title. Different industrial processes, variable use of protective equipment, and differing activities within a job title contribute to this heterogeneity in exposure.

Many studies have chosen to address exposure aggregates such as hydrocarbons or chemical industry employment. If only a subset of those agents actually affected childhood cancer risk, then the aggregation itself constitutes an additional form of misclassification.

The direction of bias from these sources of error is predictable since the same methods of imputing exposure were applied to cases and controls: the misclassification is nondifferential with respect to disease status, resulting in a bias toward the null (no association) (49). Superimposed on any underlying etiologic associations between chemical or physical agents and childhood cancer is this dilution from exposure misclassification.

Exposure classification will remain the major challenge in this research area because the rarity of childhood cancer precludes conducting true prospective studies in which exposures of parents are carefully monitored from before conception to the time of diagnosis. The challenge of retrospective exposure assignment sometimes occurring years after the time period of interest must be addressed. The limitations of occupational data from death certificates is well known (50,51), but at least some of the problems of using job titles from death certificates as exposure indicators for the study of adult cancer or other chronic diseases are not as great of a concern in using job titles from birth certificates as exposure indicators for the study of childhood cancer. The uncertainty over how recently the job was held or whether the job was held for a sufficiently lengthy period to affect disease are less problematic for studies of childhood cancer. Nonetheless, job titles from interviews with the parents are likely to be superior to job titles reported on birth certificates (52,53). In an interview, there is an opportunity to probe incomplete answers and ask about specific work activities.

The application of an exposure linkage system to aggregate occupations into exposure groups (54) as implemented by Wilkins and Sinks (44), Buckley et al. (34), and Bunin et al. (45) constitutes an improvement over purely subjective aggregations of jobs. The original motivation for developing such linkage systems was principally to aggregate diverse jobs with common exposures (54), a particular problem in studies of limited size. Inaccuracies in assigning exposures based on job titles are not avoided (55), but investigators could at least generate comparable results.

A more complete solution is to conduct detailed interviews to ascertain exposure histories, as illustrated by Guerin et al. (56). In the investigation of occupational cancers developed by Siemiatycki et al. (57), a preliminary structured interview regarding occupational exposures is followed by a semistructured interview by an industrial hygienist. This provides an opportunity for querying important aspects of exposure not identifiable through job title such as industrial processes, environmental controls, specific work locations, and responsibilities. None of the studies conducted to date have been nearly that ambitious, although an investigation devoting considerable resources to exposure assessment would be both justified by the existing literature and feasible for studies of parental occupation and childhood cancer.

Other methodological considerations are also worth noting. The constitution of the case groups varied across studies and could account for inconsistency in the results since childhood cancers are likely to have etiologic factors that vary by age at diagnosis and disease category. The isolation of very young leukemia cases by Vianna et al. (29) may have affected their results relative to other studies, either because etiologic factors are distinctive for early cases or because the recall of occupation is improved with a shorter time period of recall (from pregnancy to diagnosis). The known causal influences on childhood cancer are so limited (48) that the suggestion of etiologic specificity is based primarily on an analogy with the specificity often found for adult cancers. Until more is learned about the etiology of childhood cancers, it is preferable to conduct studies in which homogeneous subgroups of cases can be analyzed.

The precision of risk estimates remains an important concern. The rarity of childhood cancer makes it difficult for individual investigators to accumulate a sufficiently large case group to form subgroups defined by age or diagnosis with precise estimates of effect. One possible solution to this problems is for collaborative investigations to be initiated to enable inclusion of adequate numbers of cases (34). Alternatively, investigators should group both exposure and disease in a manner

allowing for aggregation across studies, for example by applying a universal occupational coding system and using a standard cancer classification system. Larger study groups will not eliminate the concerns with the accuracy of exposure definition, but could diminish the impact of random variation on the observed results and allow examination of more homogeneous case groups.

In spite of these limitations and the inconclusive results of past studies, continued evaluation of parental occupation and childhood cancer is clearly warranted. Childhood cancer exerts a major toll in years of life lost and in the psychological burden borne by the families of victims and by cancer survivors. While acknowledging the substantial methodological challenges in advancing our understanding, more sophisticated approaches to exposure assessment that have been applied to the etiology of adult cancers would be applicable to the study of childhood cancer. Future evaluations of the reproductive toxicity of environmental agents need to include carcinogenicity in the offspring, with particular emphasis on improved exposure assessment.

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